

Table of Contents for CMC Review

Tables and Figures	10
3.2.S DRUG SUBSTANCE.....	11
3.2.S DRUG SUBSTANCE.....	11
3.2.S.1 General Information	11
3.2.S.1.1 Nomenclature	11
3.2.S.1.2 Structure	11
3.2.S.1.3 General Properties.....	11
3.2.S.2 Drug Substance Manufacture	12
3.2.S.2.1 Manufacturers	12
3.2.S.2.2 Description of Manufacturing Process and Process Controls.....	12
3.2.S.2.3 Control of Materials	21
3.2.S.2.4 Controls of Critical Steps and Intermediates	25
3.2.S.2.5 Process Validation and/or Evaluation	26
3.2.S.2.6 Manufacturing Process Development	30
3.2.S.3 Characterization.....	30
3.2.S.3.1 Elucidation of Structure and Other Characteristics.....	30
3.2.S.3.2 Impurities	30
3.2.S.4 Control of Drug Substance.....	31
3.2.S.4.1 Specifications	31
3.2.S.4.2 - 3.2.S.4.3 Analytical Procedure Summaries and Validation of Analytical Procedures	32
3.2.S.4.4 Batch Analyses.....	74
3.2.S.4.5 Justification of Specifications	74
3.2.S.5 Reference Standards or Materials.....	74
3.2.S.6 and 3.2.P.2.4 Container Closure System.....	74
3.2.S.7 Stability	91
3.2.S.7.1 Stability Summary and Conclusions	91
3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment.....	113
3.2.P DRUG PRODUCT	114
3.2.P.1 Description and Composition of the Drug Product.....	114
3.2.P.2 Pharmaceutical Development.....	114
3.2.P.2.2.3 Physicochemical and biological properties.....	114
3.2.P.2.3 Manufacturing Process Development	131
3.2.S DRUG SUBSTANCE [PA2024]	148
3.2.S.2.6.4.0 COMPARABILITY DATA, b(4) PROCESS	209
3.2.S.3.1.0 Elucidation of Structure and Other Characteristics.....	210
3.2.S.3.2.1.0 PROCESS RELATED IMPURITIES IN THE PA2024 ANCILLARY COMPONENT	214
3.2.P.3.2 Batch Formula.....	249
3.2.P.4 CONTROL OF EXCIPIENTS [PA2024, REAGENT]	259
3.2.P.4.5 EXCIPIENTS OF HUMAN OR ANIMAL ORIGIN OR NOVEL EXCIPIENTS	259
3.2.P.4.6 NOVEL EXCIPIENTS	259

3.2.P.5.1 Specifications	260
3.2.P.5.2 Analytical Procedures	262
3.2.P.5.6 Justification of Specifications	266
<i>3.2.P.6 Reference Standards or Materials</i>	266
3.2.P.8.2 POST APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT	266
3.2.A Appendices b(4)	266
3.2.A.1 Facilities and Equipment	266
3.2.A.2 Adventitious Agents Safety Evaluation.....	267
3.2.R Regional Information	267
3.2.R.1 Executed Batch Records.....	267
3.2.R.2 Comparability Protocols.....	267
3.2.R.3 Methods Validation Package	267
5.3.1.4 Immunogenicity Assays (MF-J)	267
List of amendments received during BLA review period.....	268
CMC Appendix Section	269
Appendix A: List of definitions and abbreviations	269
Appendix B: Summary of clinical lot properties.....	277
Appendix C: Quartile analysis of product lots: CD54 upregulation.	286
Appendix G: Potential correlations of product qualities with infusion-related adverse events among D9901	305
Appendix H: Immune monitoring	308
Appendix I. Lot release specifications	320

Tables and Figures

Nomenclature for Sipuleucel-T.....	11
Composition of Sipuleucel-T	12
Table 3 Additional Data for Sipuleucel-T Process Monitoring.....	19
Chain of Identity Identifiers.....	20
Raw Materials for Sipuleucel-T.....	22
APH Inspection and Release Criteria	24
Parameters and acceptance criteria for process validation	28
Environmental monitoring and personnel monitoring during aseptic process validation	29
Lot Release Specifications.....	31
Phase 3 Lot Release Specifications History.....	31
b(4) method validation summary	41
b(4) method validation summary	43
b(4) method validation summary	45
Trypan blue exclusion method validation summary	48
Table Accuracy results for the final product in the b(4) validation study.....	48
b(4) method validation summary.....	50
b(4) used to analyze sipuleucel-T	114
Proportion of major cell populations in the final product for autologous vaccination into patients.....	115
Percentage of leukocyte populations at various manufacturing stages of sipuleucel-T	116
b(4) present within the starting leukapheresis material, processed cells, and the final product for autologous vaccination into patients.....	117
Upregulation of b(4) after culture with PA2024.....	119
The effect of GM-CSF on CD54 upregulation.....	120
Expression of b(4) in the CD54 positive cell population before and after ex-vivo culture with PA2024.....	121
Correlation of b(4) Markers with PA2024- b(4) Uptake.....	122
Correlation of b(4) Markers with PA2024- b(4) Uptake.....	123
Antigen presentation to PAP-specific T cell hybridomas resides in the CD54 cell population.	125
PAP antigen presentation by other cell types.....	126
Effect of GM-CSF on PAP Antigen Presentation.....	127
CD54 cell number and CD54 upregulation present in the final product.....	129
Changes in relative b(4) in the APH starting material for successive doses	129
b(4) during ex vivo culture of patient product during successive dose manufacturing	130
b(4) over successive patient doses	130
Manufacturing process changes during clinical trials.....	133